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EXAMINER	
STEADMAN, DAVID J	

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1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,300	BLACK ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9,11,12,14-16,18-22 and 29-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,11,12,14-16,18-22 and 29-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Status of the Application

[1] Claims 1-5, 7-9, 11-12, 14-16, 18-22, and 29-39 are pending in the application.

[2] Applicant's amendment to the claims, filed on 8/4/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 8/4/08, is acknowledged.

[4] Applicant's arguments filed on 8/4/08 in response to the Office action mailed on 2/4/08 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Sequence Compliance

[6] The objection to the specification as failing to comply with the sequence requirements is withdrawn in view of the specification amendment filed on 8/4/08.

Specification/Informalities

[7] Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application Nos. 09/244,984, 60/117,476, 60/135,499, and 60/073,709, fail to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Applicant states that this application is a continuation or divisional application of the prior-filed application. A continuation or divisional application cannot include new matter. Applicant is required to change the relationship (continuation or divisional application) to continuation-in-part because this application contains the following matter not disclosed in the prior-filed application: a crystalline form of a TACE polypeptide , wherein the TACE polypeptide of the polypeptide consists essentially of the amino acid sequence as shown in Table 1 (SEQ ID NO:11)" as recited in claims 29 and 37-38.

See also MPEP 602.05.(a), which states, "[i]f the examiner determines that the continuation or divisional application contains new matter relative to the prior application, the examiner should so notify the applicant in the next Office action. The examiner should also *>(A)< require a new oath or declaration along with the surcharge

set forth in 37 CFR 1.16*>(f)<; and *>(B)< indicate that the application should be redesignated as a continuation-in-part."

[8] The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: amendment to provide for antecedent basis for the limitation of a crystalline form of a TACE polypeptide , wherein the TACE polypeptide of the polypeptide consists essentially of the amino acid sequence as shown in Table 1 (SEQ ID NO:11)" as recited in claims 29 and 37-38.

[9] The specification is objected to as identifying structure coordinates of Table 1 as SEQ ID NO:1 in the specification amendment filed on 8/4/08. This appears to be a typographical error, where applicant intended to state "SEQ ID NO:11" instead of "SEQ ID NO:1".

Claim Objections

[10] The objection to claim 29 in the recitation of "polynucleotide encoding comprises" is withdrawn in view of the amendment to the claim.

[11] The objection to claim 36 in the recitation of "the crystalline form the crystalline form" is withdrawn in view of the amendment to the claim.

[12] Claims 5, 15, 32, and 39 are objected to and in the interest of substantially improving claim form, it is suggested that the phrase "the TACE polypeptide consists of the expression product of a polynucleotide encoding amino acid residues 1-477 of TACE as set forth in SEQ ID NO:8, and wherein the expression product…is fused to the C-terminus of the expression product" be amended to recite, *e.g.,* "the TACE polypeptide consists of the expression product of a polynucleotide encoding amino acid residues 1-477 of TACE as set forth in SEQ ID NO:8, except Ser266 of SEQ ID NO:8 is changed to Ala, Asn452 of SEQ ID NO:8 is changed to Gln, and the amino acid sequence of SEQ ID NO:2 is fused to the C-terminus of the expression product"

Claim Rejections - 35 USC § 112, Second Paragraph

[13] The rejection of claims 4-5 under 35 U.S.C. 112, second paragraph, as being confusing in that it is unclear as to the intended scope of TACE polypeptides that are encompassed by the claims is withdrawn in view of the amendment to the claims.

[14] The rejection of claims 14 and 30 under 35 U.S.C. 112, second paragraph, as being confusing in the recitation of "crystal has the structure coordinates according to Table 1" is withdrawn in view of the amendment to the claims.

[15] The rejection of claims 20-21 under 35 U.S.C. 112, second paragraph, as being unclear in the recitation of "the solution comprising the TACE polypeptide and the

binding partner is at a concentration of…" is withdrawn in view of the amendment to the claims.

Claim Rejections - 35 USC § 112, First Paragraph

[16] Claims 29-31 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163.II.A.3.(b) states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description". According to MPEP § 2163.I.B, "While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure" and "The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117".

Claims 29 (claims 30-31 dependent therefrom), 37, and 38 recite the limitation, "the TACE polypeptide consists essentially of the amino acid sequence as shown in

Table 1 (SEQ ID NO:11)". The specification appears to provide adequate descriptive support for a crystal of SEQ ID NO:8 or variant thereof with Ser266 changed to Ala, Asn452 changed to Gln, and the amino acid sequence of SEQ ID NO:2 is fused to the C-terminus. The instant remarks at p. 9, middle point to Table 1 as providing support for the limitation at issue. However, while Table 1 would appear to provide adequate descriptive support for the TACE protein of the crystal having the *structural coordinates* of Table 1, the structural coordinate data would not appear to support a crystalline form of a polypeptide of SEQ ID NO:11, particularly as the specification discloses that it is the SEQ ID NO:8 variant as noted above that was used to obtain the structural coordinates of Table 1 (see specification Example 2 at pp. 33-34). Moreover, it is noted that an alignment between SEQ ID NO:8 and SEQ ID NO:11 (see Appendix A) reveals a mismatch at position 452 of SEQ ID NO:8, corresponding to position 234 of SEQ ID NO:11. Applicant is invited to show descriptive support for the limitation at issue.

[17] The new matter rejection of claims 15-16 and 18-21 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment to claim 15 to recite buffers that appear to correspond to buffers B), C), and D) as set forth at pp. 33-34 of the specification.

[18] The written description rejection of claims 1-5, 7-9, 11-12, 14-16, 18-22, and 29-36 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See,

e.g., paragraph 13 beginning at p. 7 of the Office action mailed on 7/25/06; paragraph 15 beginning at p. 7 of the Office action mailed on 2/27/07; and paragraph 16 beginning at p. 9 of the Office action mailed on 2/4/08. Newly added claims 37-39 have been included in the instant rejection for reasons of record and reasons set forth below. Thus, claims 1-5, 7-9, 11-12, 14-16, 18-22, and 29-39 are rejected herein.

RESPONSE TO ARGUMENT: Beginning at p. 11 of the instant remarks, applicant argues the claimed crystals and method are adequately described given the claim limitations, the disclosure and working examples of the specification, and the hypothetical claim 1 of case 4 of the Trilateral Report.

Applicant's argument is not found persuasive. Initially, it is noted that applicant states, "It is undisputed that the scope of claims 1 and 22 is commensurate with the TACE crystal species disclosed by the Applicants" and "It is also undisputed that claims 1 and 22 in their present form impose almost identical structural parameters as those specified by hypothetical claim 1 exemplified in case 4" of the Trilateral Report (instant remarks at p. 13, top). However, contrary to applicant's statements, and as noted in the prior Office action, the genus of crystal of claims 1 and 22 is not adequately described by the single disclosed representative species and, as further noted in the prior Office action, the claims of this case are not seen as imposing "almost identical structural parameters" as claim 1 of case 4 of the Trilateral Report.

The examiner maintains the position that the disclosure of the specification, including the single disclosed representative species of TACE crystals, *i.e.,* a crystal of the mutant TACE of SEQ ID NO:8, except Ser266 changed to Ala, Asn452 changed to

Gln and the sequence Gly-Ser-$(His)_6$ directly fused to the C-terminus in complex with N-[D,L-[2-(hydroxyaminocarnbonyl)methyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41° and the single disclosed method for crystallization as set forth at Example 2 (pp. 33-34 of the specification) fails to adequately describe the genus of claimed crystals and methods.

Based on the claims and the disclosure of the specification, it would appear that the genus of TACE polypeptides of the crystalline form are not limited to the single TACE polypeptide that achieved crystallization. See, *e.g.,* claim 4 and the genus of hydroxamate-based binding partners would appear to encompass any "binding partner" that is based upon a hydroxamate structure (see Appendix A). As such, each genus encompasses widely variant species of "TACE" polypeptides and "hydroxamate-based" binding partners. However, other than the single disclosed representative species as noted above, the specification fails to disclose any additional species of the genus of crystalline TACE proteins, optionally in complex with any hydroxamate-based binding partners, and crystallization conditions, which combine to achieve a crystal with the recited characteristic(s) of the claimed crystal. While applicant argues that TACE polypeptides were known at the time of the invention, there is no indication in the claims or specification that the TACE polypeptide of the crystal is intended as being limited to those that were known in the art at the time of the invention. To the contrary, based upon the specification's disclosure, it appears the genus of crystals is intended as encompassing mutants and variants of a known TACE polypeptide, particularly as the

specification fails to disclose even a single representative species of crystal of a *known* TACE and instead the single representative species of crystal is a *mutant* TACE.

As noted above, it was well-known at the time of the invention that protein crystallography was a highly unpredictable art. See, *e.g.,* the teachings of McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990), which states (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out, trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual." See also the cited teachings of

Branden et al., Drenth et al., Kierzek et al., and Wiencek as set forth in the Office action filed on 7/25/06. That protein crystallography was highly unpredictable does not appear to be disputed by applicant.

With respect to the Trilateral Report, as noted in the prior Office action, in contrast to claim 1 of Case 4 of the Trilateral Report, the genus of compositions encompasses crystalline TACE polypeptides and hydroxamate-based binding partners with undefined structure. Also, it is noted that the hypothetical examples in the Trilateral Report are given to provide *guidance* with respect to patentability, they are not to be taken as rigid test.

While it is acknowledged that claims 2-5, 7-9, 11-12, 14, 16, 18-21, and 29-39 recite additional limitations, the examiner maintains the position that the specification fails to adequately describe the claimed composition, particularly with respect to the genus of TACE polypeptides, hydroxamate-based binding partners, and crystallization conditions. Claims 4-5, 29, 15, and 32 limit the TACE polypeptide to being the "expression product" of a polynucleotide encoding residues 1-477 of TACE of SEQ ID NO:8 or variant thereof as encompassed by the claims. However, it is noted that since the polynucleotide of the claim is open to encoding any additional amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of SEQ ID NO:8, the TACE polypeptide of these claims can have any additional amino acids added thereto. Put another way, the claim has been interpreted as requiring that the polynucleotide encode *at least* residues 1-477 of SEQ ID NO:8 (or recited variant thereof), but can additionally encode amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of

SEQ ID NO:8. Also, with respect to claims 7, 22, 32, it is noted that the genus of "hydroxamate-based" binding partners is interpreted as encompassing any compound having a hydroxamate group.

Other than the single disclosed representative species, the specification fails to disclose any additional species of the genus of crystalline TACE proteins, optionally in complex with any hydroxamate-based binding partners, to achieve formation of a crystal having the disclosed characteristics. In other words, other than the single disclosed representative species, there is no disclosed correlation between the sequence of a TACE polypeptide, the structure of an optional ligand, and/or the conditions for crystallization that will achieve formation of a crystal as encompassed by the claims. As noted by Branden et al. (*supra*), "The formation of crystals is also critically dependent on a number of different parameters, including…added…legends to the protein" and McPherson points out that trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by "no more than one or just a few amino acids" can result in significant influences upon the change in which variables are important for successful crystallization. That structurally similar polypeptides do not form crystals with similar crystal structures is evidenced by Ingram et al. (*Prot. Eng. Design Select.* 19:155-161, 2006), which teaches crystallization of a TACE catalytic domain with a V353G mutation. According to Ingram, the TACE crystal reported by Maskos et al., which appears to correspond to the instant disclosure, "was found to be unsuitable for iterative structure-based design studies" and reports crystals of a TACE catalytic domain with a V353G mutation in complex with inhibitor crystallized in a buffer

0.1M sodium citrate and having space group $P2_12_12_1$ and unit cell dimensions that are distinct from the single disclosed representative species of the specification (p. 157, column 2). See also the cited teachings of Drenth et al., Kierzek et al., and Wiencek as set forth in the Office action filed on 7/25/06. That protein crystallography was highly unpredictable, even among proteins that are structurally similar with respect to their amino acid sequences does not appear to be disputed by applicant.

While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". Given the high level of unpredictability associated with protein crystallography and the lack of description of a representative number of species to reflect the variation among members of the genus, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

It is acknowledged that claim 39 is limited with respect to the polypeptide, binding partner, space group, and unit cell dimensions, however, it is noted that the recited binding partner is not the same as that of the single disclosed species (compare the binding partner at Example 2, p. 33, lines 16-17 with the recited binding partner of claim 39) and as noted above, there is no disclosed or art recognized correlation between the recited polypeptide and binding partner and the ability to form a crystal having the

recited space group and unit cell dimensions, particularly in view of the unpredictability associated with crystallography as supported by the references of record.

[19] The scope of enablement rejection of claim(s) 1-5, 7-9, 11-12, 14-16, 18-22, and 29-36 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See, *e.g.,* paragraph 14 beginning at p. 9 of the Office action mailed on 7/25/06; paragraph 16 beginning at p. 12 of the Office action mailed on 2/27/07; and paragraph 17 beginning at p. 18 of the Office action mailed on 2/4/08. Newly added claims 37-39 have been included in the instant rejection for reasons of record and reasons set forth below. Thus, claims 1-5, 7-9, 11-12, 14-16, 18-22, and 29-39 are rejected herein.

RESPONSE TO ARGUMENT: Beginning at p. 18 of the instant remarks, in addressing the breadth of the claimed crystals and methods, applicant argues the claimed crystals and method are enabled because the scope of the claimed crystals and method is commensurate in scope with the disclosure of the specification and claim 1 of case 4 of the Trilateral Report.

Applicant's argument is not found persuasive. As noted in a prior Office action, claims 1, 7, and 22 are drawn to a composition comprising a crystalline form of a TACE polypeptide, optionally in complex with any "hydroxamate-based" binding partner, wherein the structure(s) of the TACE polypeptide and/or "hydroxamate-based" binding partner is/are unlimited and is interpreted as encompassing mutants and variants of TACE, particularly as the single disclosed working example is a crystal of a mutant

TACE polypeptide. Although applicant argues claims 1 and 22 are limited to the single working example, it appears applicant is narrowly interpreting the claimed crystal as being limited to the polypeptide of SEQ ID NO:8, except Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus and the binding partner of N-[D,L-[2-(hydroxyaminocarnbonyl)methyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine. However, such limitations are not present and have not been improperly imported into the claims.

Claims 4-5, 29, and 32 limit the TACE polypeptide to being the expression product of a polynucleotide encoding residues 1-477 of TACE of SEQ ID NO:8. However, it is noted that since the polynucleotide of the claim is open to encoding any additional amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of SEQ ID NO:8, the TACE polypeptide of these claims can have any additional amino acids added thereto. Put another way, the claim has been interpreted as requiring that the polynucleotide encode *at least* residues 1-477 of SEQ ID NO:8, but can additionally encode amino acids at the N-terminal and/or C-terminal end(s) of amino acids 1-477 of SEQ ID NO:8. Similarly, claims 29 and 37-38 limit the scope of TACE polypeptides to consisting essentially of SEQ ID NO:11, wherein the transitional phrase “consists essentially of” has been interpreted as being equivalent to comprising and thus the polypeptide encompasses any additional amino acids at the N- and/or C-terminus of SEQ ID NO:11.

Also, with respect to claims 7, 22, and 32, it is noted that the genus of "hydroxamate-based" binding partners is interpreted as encompassing any compound having a hydroxamate group (see Appendix A).

It is noted that claim 32 is unlimited with respect to the unit cell dimensions of the crystal.

Claim 15 is so broad as to encompass a method for crystallizing the expression product of a polynucleotide encoding residues 1-477 of TACE of SEQ ID NO:8, wherein the "expression product" can have any additional N-terminal and/or C-terminal amino acids as noted above, the structure of the "hydroxamate-based" binding partner is unlimited, and a crystallization buffer as encompassed by the claims.

The broad scope of claimed crystals and crystallization methods is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to a crystal of the mutant TACE of SEQ ID NO:8 with Ser266 changed to Ala, Asn452 changed to Gln, and the sequence Gly-Ser-$(His)_6$ fused directly to the C-terminus, co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, $\beta=107.41^{o}$ produced according to the method set forth in the specification at pp. 33-34 using crystallization buffer D, *i.e.,* 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol.

It is acknowledged that claim 39 is limited with respect to the polypeptide, binding partner, space group, and unit cell dimensions, however, it is noted that the recited

binding partner is not the same as that of the single disclosed species (compare the binding partner at Example 2, p. 33, lines 16-17 with the recited binding partner of claim 39) and as noted above, there is no disclosed or art recognized correlation between the recited polypeptide and binding partner and the ability to form a crystal having the recited space group and unit cell dimensions, particularly in view of the unpredictability associated with crystallography as supported by the references of record.

Beginning at p. 22 of the instant remarks, in addressing the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, applicant argues that by following the Example 2 conditions, it would be routine experimentation to make and use all crystals and methods as encompassed by the claims, citing to the teachings of the Itoh and Sauer references.

Applicant's argument is not found persuasive. As noted in the prior Office action, the state of the art at the time of the invention acknowledges a high level of unpredictability for making a protein crystal with an expectation that the crystal will be of diffraction quality. The reference of Branden et al. (cited in the PTO-892 mailed on 7/25/06) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. (cited in the PTO-892 mailed on 7/25/06) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict

a priori those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (cited in the PTO-892 mailed on 7/25/06), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). In view of these teachings, there is no expectation that a skilled artisan can use the disclosed crystallization conditions to achieve diffraction quality crystals of other TACE polypeptides. Also, Wiencek (cited in the PTO-892 mailed on 7/25/06) teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units…some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). Additionally, Buts et al. (*Acta Cryst* D61:1149-1159, 2005) teaches that "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization." "Five naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution." Specifically, the reference of Buts *et al.* teaches that the F17e-G and F17f-G adhesins differ in only one amino acid from the F17c-G adhesin, Arg21Ser and His36Tyr, respectively, and yet these proteins that are 99% identical in sequence resulted in different crystal forms with distinct diffraction properties (see Tables 1-3). See also the teachings of McPherson as

set forth above. Applicant does not appear to dispute the objective evidence of these references.

Even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. *Cell. Mol. Life Sci*. 2004, 61: 525-536) and currently there are no directed methods which makes this process any easier or more predictable. Thus, each protein that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see Weber, *Methods in Enzymology*, 1997, Vol. 276, pp. 13-22). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a role in obtaining crystallization

conditions despite the extremely high skill level of those in the art (see Drenth, *supra,* Cudney, *Rigaku Journal*, 1999, Vol. 16, No. 1, pp. 1-7).

When these teachings are taken as a whole, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other TACE polypeptides optionally having a desired space group and unit cell dimensions as encompassed by the claims can be achieved using *any* crystallization parameters as encompassed by the claims. Further, it is noted that the asserted utility of the claimed crystal is for determination of the structure of TACE for structure based design of TACE inhibitors (p. 2, first full paragraph), which is undisputed by applicant, and it is highly unpredictable as to whether mutant and variant TACE polypeptides will maintain a three-dimensional structure that is equivalent to wild-type TACE for design of biologically relevant TACE inhibitors. That structurally similar polypeptides do not form crystals with similar crystal structures is evidenced by Ingram et al. (*Prot. Eng. Design Select.* 19:155-161, 2006), which teaches crystallization of a TACE catalytic domain with a V353G mutation. According to Ingram, the TACE crystal reported by Maskos et al. "was found to be unsuitable for iterative structure-based design studies" and reports crystals of a TACE catalytic domain with a V353G mutation in complex with inhibitor crystallized in a buffer 0.1M sodium citrate and having space group $P2_12_12_1$ and unit cell dimensions that are distinct from the single working example of the specification (p. 157, column 2).

Although applicant maintains that the Ihto and Sauer references provide evidence that similar amino acid sequences would form similar crystals, there is no

evidence that the teachings of Ihto and Sauer are relevant to a TACE polypeptide. Instead, the teachings of Ingram are directly relevant to TACE and while applicant notes that the mutation in Ingram is disclosed as inducing a conformation change and as long as variants do not induce such conformational changes, one would expect similar amino acids to readily crystallize, it is noted that the scope of TACE polypeptides and optional binding partners is not limited to those that do not induce a conformation change and the specification and prior art appear to be silent regarding any guidance as to those mutants and/or binding partners that do not induce a conformation change.

While applicant argues the cited references are not relevant to the instant disclosure, it is noted that because applicant has demonstrated successful crystallization of only a single TACE amino acid sequence with a single binding partner under a single set of crystallization conditions, contrary to applicant's assertion, the teachings of the references directly support the examiner's position of unpredictability in protein crystallization, particularly as there is no evidence of record that a *TACE polypeptide* is not subject to such unpredictability in crystallization.

Conclusion

[20] Status of the claims:

Claims 1-5, 7-9, 11-12, 14-16, 18-22, and 29-39 are pending.

Claims 1-5, 7-9, 11-12, 14-16, 18-22, and 29-39 are rejected.

No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
Primary Examiner, Art Unit 1656

APPENDIX A

Query sequence 1

```
>SEQ ID NO:8
MRQSLLFLTSVVPFVLAPRPPDDPGFGPHQRLEKLDSLLSDYDILSLSNIQQHSVRKRDL
QTSTHVETLLTFSALKRHFKLYLTSSTERFSQNFKVVVVDGKNESEYTVKWQDFFTGHVV
GEPDSRVLAHIRDDDVIIRINTDGAEYNIEPLWRFVNDTKDKRMLVYKSEDIKNVSRLQS
PKVCGYLKVDNEELLPKGLVDREPPEELVHRVKRRADPDPMKNTCKLLVVADHRFYRYMG
RGEESTTTNYLIELIDRVDDIYRNTSWDNAGFKGYGIQIEQIRILKSPQEVKPGEKHYNM
AKSYPNEEKDAWDVKMLLEQFSFDIAEEASKVCLAHLFTYQDFDMGTLGLAYVGSPRANS
HGGVCPKAYYSPVGKKNIYLNSGLTSTKNYGKTILTKEADLVTTHELGHNFGAEHDPDGL
AECAPNEDQGGKYVMYPIAVSGDHENNKMFSNCSKQSIYKTIESKAQECFQERSNKV
```

```
Query sequence 2

>SEQ ID NO:11
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IEQIRILKSPQEVKPGEKHYNMAKSYPNEEKDAWDVKMLLEQFSFDIAEEASKVCLAHLF
TYQDFDMGTLGLAYVGSPRANSHGGVCPKAYYSPVGKKNIYLNSGLTSTKNYGKTILTKE
ADLVTTHELGHNFGAEHDPDGLAECAPNEDQGGKYVMYPIAVSGDHENNKMFSQCSKQSI
YKTIESKAQECFQERS
```

Full-length alignment between two sequences

```
>>SEQ ID NO:11                                              (256 aa)
 s-w opt: 1729  Z-score: 2119.3  bits: 400.6 E(): 3.1e-116
Smith-Waterman score: 1729;  99.219% identity (99.219% ungapped) in 256 aa overlap (219-474:1-
256)

      190       200       210       220       230       240
SEQ    VDNEELLPKGLVDREPPEELVHRVKRRADPDPMKNTCKLLVVADHRFYRYMGRGEESTTT
                                    :::::::::::::::::::::::::::::
SEQ                                 DPMKNTCKLLVVADHRFYRYMGRGEESTTT
                                            10        20        30

      250       260       270       280       290       300
SEQ    NYLIELIDRVDDIYRNTSWDNAGFKGYGIQIEQIRILKSPQEVKPGEKHYNMAKSYPNEE
       ::::::::::::::::.:::::::::::::::::::::::::::::::::::::::::::
SEQ    NYLIELIDRVDDIYRNTAWDNAGFKGYGIQIEQIRILKSPQEVKPGEKHYNMAKSYPNEE
              40        50        60        70        80        90

      310       320       330       340       350       360
SEQ    KDAWDVKMLLEQFSFDIAEEASKVCLAHLFTYQDFDMGTLGLAYVGSPRANSHGGVCPKA
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    KDAWDVKMLLEQFSFDIAEEASKVCLAHLFTYQDFDMGTLGLAYVGSPRANSHGGVCPKA
             100       110       120       130       140       150

      370       380       390       400       410       420
SEQ    YYSPVGKKNIYLNSGLTSTKNYGKTILTKEADLVTTHELGHNFGAEHDPDGLAECAPNED
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    YYSPVGKKNIYLNSGLTSTKNYGKTILTKEADLVTTHELGHNFGAEHDPDGLAECAPNED
             160       170       180       190       200       210

      430       440       450       460       470
SEQ    QGGKYVMYPIAVSGDHENNKMFSNCSKQSIYKTIESKAQECFQERSNKV
       :::::::::::::::::::::::.::::::::::::::::::::::::::
SEQ    QGGKYVMYPIAVSGDHENNKMFSQCSKQSIYKTIESKAQECFQERS
             220       230       240       250
```